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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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ART UNIT	**PAPER NUMBER**
1636	12

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/834,778	SILVER ET AL.	
	Examiner	Art Unit	Paper No. 12
	Daniel M Sullivan	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 August 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-50* is/are pending in the application.

4a) Of the above claim(s) *22-50* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 April 2001* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *9* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

This Non-Final Office Action is a response to the Amendment and Response filed August 12, 2002 (Paper No. 11) and Information Disclosure Statement filed May 9, 2002 (Paper No. 9). Claims 1-50 are pending in the Application. Claims 22-50 were withdrawn from consideration in Paper No. 8 as being directed to a non-elected invention.

Drawings

The drawings are objected to for the reasons provided in the form PTO-948 accompanying Paper No. 8. A proposed drawing correction or corrected drawings are required in reply to the Office action to avoid abandonment of the application. The objection to the drawings will not be held in abeyance.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. Correction of Informalities -- 37 CFR 1.85

New corrected drawings must be filed with the changes incorporated therein. Identifying indicia, if provided, should include the title of the invention, inventor's name, and application number, or docket number (if any) if an application number has not been assigned to the application. If this information is provided, it must be placed on the front of each sheet and centered within the top margin. If corrected drawings are required in a Notice of Allowability (PTOL-37), the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability." Extensions of time may NOT be obtained under the provisions of 37 CFR 1.136 for filing the corrected drawings after the mailing of a Notice of Allowability. The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. Corrections other than Informalities Noted by Draftsperson on form PTO-948.

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red

ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the time period set in the Office action. See 37 CFR 1.185(a). Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

Response to Arguments

Claim Rejections - 35 USC § 112

Rejection of claims 1-21 under 35 U.S.C. § 112, first paragraph, in Paper No. 8 as lacking enablement for use for therapeutic purposes in *in vivo* controlled delivery of diagnostic and therapeutic agents is withdrawn. The claims are drawn to a product having many uses that are enabled by the teachings of the specification and prior art, as evidenced in Paper No. 9. Although the examiner is correct to point out that the disclosure is not enabling for claims directed to gene therapy or *in vivo* diagnostics, the claims are not limited to such uses; therefore the skilled artisan would know how to use the claimed product, such as in the production of a transgenic plant or mouse, without undue experimentation.

Claim Rejections - 35 USC § 103

Rejection of claims 1-21 under 35 U.S.C. § 103 as being unpatentable over Sauer (1996) *Nucleic Acids Res.* 24:4608-4613 and Gagneten *et al.* (1997) *Nucleic Acids Res.* 25:3326-3331 in view of Miyoshi *et al.* (1998) *J. Virol.* 72:8150-8157 is withdrawn. Applicants argue

persuasively in Paper No. 11 that the combined teachings of the cited art would not produce the claimed invention.

New Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are directed to a nucleic acid sequences, or a cell comprising said nucleic acid sequences, comprising a "signal sequence recognized by a recombinase" (e.g. claim 1) or a "signal site" (e.g. claim 2). Although it appears that Applicant intends that the terms "signal sequence" and "signal site" be interchangeable, the disclosure does not explicitly state that the terms have the same meaning and, in fact, on page 5, line 14, of the specification the terms are used in the alternative suggesting that they are not equivalent. The claims are indefinite because the disclosure does not provide a definition of the terms "signal site" and "signal sequence" that would allow one to ascertain how the metes and bounds of the claims that recite "signal site" differ from claims that recite "signal sequence". Furthermore, there is insufficient antecedent basis for the term "signal site" or "signal sequence" in many of the claims depending from claims 1 or 2 because the dependent claim recites "signal site" when the base claim recites "signal sequence" and *vice versa*. This is inescapably true for claims that depend from both

claims 1 and 2 (e.g. claim 5). It is suggested that Applicant amend the claims to recite only "signal sequence", as the disclosure clearly favors the term "signal sequence" when referring to the target sequence for site-specific recombination.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 2, 5-13 and 18-20 are rejected under 35 U.S.C.§ 102(b) as being anticipated by Anderson (1997; IDS #A2) as evidenced by Kilby *et al.* (1993; IDS #C22).

Claim 1 is directed to a nucleic acid molecule comprising a sequence encoding a recombinase and a signal sequence recognized by said recombinase. Claim 2 is directed to a nucleic acid molecule comprising at least a first signal site and a second signal site and a recombinase gene operably linked to an expression control sequence, said first and second signal sites being positioned to mediate excision of a sufficient portion of either the recombinase gene or the expression control sequence to extinguish recombinase activity when the first and second signal sites are contacted with a recombinase. Claim 5 limits the recombinase of claims 1 or 2, to a *cre* recombinase or an Flp recombinase and the signal site of claims 1 or 2 to lox sites or FRT sites. Claim 6 limits the nucleic acid molecule of claim 1 to a nucleic acid molecule comprising two signal sequences that are recognized by said recombinase and are positioned with respect to said sequence encoding said recombinase so that recombination by said recombinase inactivates or decreases expression of said recombinase. Claim 7 limits the nucleic acid molecule of claim 6,

to a nucleic acid molecule wherein said signal sequences flank said sequence encoding said recombinase or a positive regulatory element of said sequence encoding said recombinase.

Anderson teaches a nucleic acid molecule comprising a first recombinase signal sequence and a second recombinase signal sequence (i.e. RTS), and a recombinase gene operably linked to an expression control sequence (i.e. inducible promoter; see especially Figures 3C and 6B). The signal sequences of Anderson are positioned flanking the recombinase encoding sequence and the expression control sequence such that expression of the recombinase results in excision of the recombinase gene and expression control sequence thus extinguishing recombinase activity. The loss of recombinase activity upon excision is evidenced by the teachings of Kilby *et al.* who teaches, "the small circular molecule [produced upon excision of a nucleic acid by a site-specific recombinase]...would be quickly lost *in vivo*" (page 413, column 2, first full paragraph). In the third full paragraph of column 4, Anderson teaches that the recombinase target sites can be LoxP sites or FRT sites, and one of ordinary skill would understand that the use of these sites dictates that the recombinase used be either *cre* or Flp, respectively. Anderson teaches a nucleic acid sequence having all of the limitations of the instant claims; therefore the claims are anticipated by Anderson.

Claim 8 is directed to cell comprising the nucleic acid molecule of any one of claims l, 2 or 6. Claim 9 limits the cell of claim 8, to a cell further comprising a second nucleic acid molecule comprising a target gene and signal sequences recognized by said recombinase. Claim 10 limits the cell of claim 9, to a cell wherein said recombinase, when expressed in said cell, excises or inverts a sequence in said second nucleic acid molecule that is located between said signal sequences in said second nucleic acid molecule, and the excision or inversion results in

modulation of expression of said target gene. Claim 11 limits the cell of claim 10 to a cell wherein said signal sequences in said second nucleic acid molecule are in direct orientation with respect to one another; claim 12 limits the cell of claim 11, to a cell wherein said signal sequences in said second nucleic acid molecule flank said target gene; and claim 13 is directed to the cell of claim 11, wherein said signal sequences in said second nucleic acid molecule flank a positive regulatory element of said target gene. Claim 18 is directed to the cell of claim 8, wherein said signal sequences in said nucleic acid molecule comprising said sequence encoding said recombinase flank said nucleic acid sequence encoding said recombinase. Claim 19 limits the cell of claim 8 to a cell wherein said signal sequences in said nucleic acid molecule comprising said sequence encoding said recombinase flank a positive regulatory element of said nucleic acid sequence encoding recombinase and claim 20 is directed to the cell of claim 9, wherein said nucleic acid molecule comprising said sequence encoding said recombinase and said second nucleic molecule are present in the same vector.

The nucleic acid molecules taught by Anderson further comprise one or more nucleic acid molecules encoding non-recombinase proteins positioned between recombinase signal sequences such that expression of the recombinase excises said one or more nucleic acid molecules encoding non-recombinase proteins (see especially Figures 3C and 6B). The skilled artisan would understand that the teaching of Anderson to position the recombinase signal sequences for excision of an intervening nucleic acid molecule indicates direct orientation with respect to one another. In the first sentence of column 6, Anderson teaches that, "cell lines may be made by transforming at least one cell with nucleic acid comprising the constructs of the invention". The cell lines of Anderson anticipate the cell claimed in the instant Application.

Claims 1-8 are rejected under 35 U.S.C.§102(b) as being anticipated by either one of Choulika *et al.* (1997; WO 97/06271; evidenced by Choulika *et al.* (2001; IDS #A7)) or Russ *et al.* (1996; IDS #C52) as evidenced by Kilby *et al.* (1993; IDS #C22).

The limitations of claims 1, 2 and 5-8 are recited above. Claim 3 is directed to the nucleic acid molecule of claims 1 or 2, wherein said nucleic acid molecules are included in a retroviral vector and said signal sequence is inserted into a retroviral long terminal repeat of said vector and claim 4 limit insertion of the signal sequence in the nucleic acid of claim 3 to insertion into the U3 region of the 3' retroviral long terminal repeat of said vector, or the U5 region of the 5'LTR, or the R region.

Choulika *et al.* and Russ *et al.* teach a nucleic acid molecule comprising a first recombinase signal sequence and a second recombinase signal sequence (i.e. *loxP*), and a recombinase gene operably linked to an expression control sequence (i.e. see especially Figure 4 in Choulika *et al.* and Figure 3 in Russ *et al.*). The signal sequences of Choulika *et al.* and Russ *et al.* are positioned flanking the recombinase encoding sequence and the expression control sequence such that expression of the recombinase results in excision of the recombinase gene and expression control sequence thus extinguishing recombinase activity. As described herein above, the loss of recombinase activity upon excision is evidenced by the teachings of Kilby *et al.* Choulika *et al.* further teaches that the recombinase system used can be CreLox sites or FLP (see especially column 6, paragraph 4 of IDS #A7). The nucleic acid taught by Choulika *et al.* and Russ *et al.* is comprised within a retroviral vector and said signal sequence is inserted into the U3 region of the 3' retroviral long terminal repeat (see especially the Abstract of Choulika *et al.* and the first paragraph on page 4928 of Russ *et al.*). Choulika *et al.* and Russ *et al.* therefore

teach a nucleic acid sequence having all of the limitations of the instant claims and further teach that the retroviral vector can be used to transduce cells (see especially column 11, Example 4(c) of Choulika *et al.* and the first paragraph in the second column on page 4928 of Russ *et al.*). The teachings of Choulika *et al.* and Russ *et al.* therefore anticipate the claims of the instant application.

Claims 1, 2, 5-13 and 18-20 are rejected under 35 U.S.C.§ 102(a) as being anticipated by Bunting *et al.* (1999; IDS #C53) as evidenced by Kilby *et al.* (1993; IDS #C22).

The limitations of the claims are recited herein above. Bunting *et al.* teaches a nucleic acid molecule comprising a first recombinase signal sequence and a second recombinase signal sequence (i.e. *loxP*), and a recombinase gene (i.e. *Cre*) operably linked to an expression control sequence (i.e. tACE promoter; see especially Figure 2 and the caption thereto). The signal sequences of Bunting *et al.* are positioned flanking the recombinase encoding sequence and the expression control sequence such that expression of the recombinase results in excision of the recombinase gene and expression control sequence thus extinguishing recombinase activity. The loss of recombinase activity upon excision is evidenced by the teachings of Kilby *et al.* described herein above Anderson teaches a nucleic acid sequence having all of the limitations of the instant claims; therefore the claims are anticipated by Anderson.

The nucleic acid molecule taught by Bunting *et al.* further comprises a nucleic acid molecules a neomycin resistance gene positioned between recombinase signal sequences such that expression of the recombinase excises said neomycin resistance gene (see especially Figure 2 and the caption thereto). The skilled artisan would understand that the teaching of Bunting *et*

al. to position the recombinase signal sequences for excision of an intervening nucleic acid molecule indicates direct orientation with respect to one another. In the second full paragraph on page 1527, Bunting *et al.* teaches transformation of ES cells with the described nucleic acid. The ES cells of Bunting *et al.* therefore anticipate the cell claimed in the instant Application.

Allowable Subject Matter

Claims 14-17 and 21 would be allowable if rewritten to overcome the rejection(s) under 35 U.S.C.§112, second paragraph, set forth in this Office action and to include all of the limitations of the base claim and any intervening claims.

Conclusion

None of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
October 17, 2002

JAMES KETTER
PRIMARY EXAMINER